

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Faslodex 250 mg solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled syringe contains 250 mg fulvestrant in 5 ml solution.

Excipients with known effect:

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to yellow, viscous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Faslodex is indicated for the treatment of postmenopausal women with estrogen receptor positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant anti-estrogen therapy, or disease progression on therapy with an anti-estrogen.

4.2 Posology and method of administration

Posology

Adult females (including the elderly)

The recommended dose is 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose.

Special population

Renal impairment

No dose adjustments are recommended for patients with mild to moderate renal impairment (creatinine clearance ≥ 30 ml/min). Safety and efficacy have not been evaluated in patients with severe renal impairment (creatinine clearance < 30 ml/min), and, therefore, caution is recommended in these patients (see section 4.4).

Hepatic impairment

No dose adjustments are recommended for patients with mild to moderate hepatic impairment. However, as fulvestrant exposure may be increased, Faslodex should be used with caution in these patients. There are no data in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

Paediatric population

The safety and efficacy of Faslodex in children from birth to 18 years of age have not been established. Currently available data are described in sections 5.1 and 5.2, but no recommendation on a posology can be made.

Method of administration

Faslodex should be administered as two consecutive 5 ml injections by slow intramuscular injection (1-2 minutes/injection), one in each buttock.

For detailed instructions for administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy and lactation (see section 4.6).

Severe hepatic impairment (see sections 4.4 and 5.2).

4.4 Special warnings and precautions for use

Faslodex should be used with caution in patients with mild to moderate hepatic impairment (see sections 4.2, 4.3 and 5.2).

Faslodex should be used with caution in patients with severe renal impairment (creatinine clearance less than 30 ml/min).

Due to the intramuscular route of administration, Faslodex should be used with caution if treating patients with bleeding diatheses, thrombocytopenia or those taking anticoagulant treatment.

Thromboembolic events are commonly observed in women with advanced breast cancer and have been observed in clinical trials with Faslodex (see section 4.8). This should be taken into consideration when prescribing Faslodex to patients at risk.

There are no long-term data on the effect of fulvestrant on bone. Due to the mechanism of action of fulvestrant, there is a potential risk of osteoporosis.

Paediatric population

Faslodex is not recommended for use in children and adolescents as safety and efficacy have not been established in this group of patients (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

A clinical interaction study with midazolam (substrate of CYP3A4) demonstrated that fulvestrant does not inhibit CYP3A4. Clinical interaction studies with rifampicin (inducer of CYP3A4) and ketoconazole (inhibitor of CYP3A4) showed no clinically relevant change in fulvestrant clearance. Dose adjustment is therefore not necessary in patients who are receiving fulvestrant and CYP3A4 inhibitors or inducers concomitantly.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Patients of child-bearing potential should be advised to use effective contraception while on treatment.

Pregnancy

Faslodex is contraindicated in pregnancy (see section 4.3). Fulvestrant has been shown to cross the placenta after single intramuscular doses in rat and rabbit. Studies in animals have shown reproductive toxicity including an increased incidence of foetal abnormalities and deaths (see section 5.3). If pregnancy occurs while taking Faslodex, the patient must be informed of the potential hazard to the foetus and potential risk for loss of pregnancy.

Breastfeeding

Breastfeeding must be discontinued during treatment with Faslodex. Fulvestrant is excreted in milk in lactating rats. It is not known whether fulvestrant is excreted in human milk. Considering the potential for serious adverse reactions due to fulvestrant in breast-fed infants, use during lactation is contraindicated (see section 4.3).

Fertility

The effects of Faslodex on fertility in humans has not been studied.

4.7 Effects on ability to drive and use machines

Faslodex has no or negligible influence on the ability to drive or use machines. However, since asthenia has been reported very commonly with Faslodex, caution should be observed by those patients who experience this adverse reaction when driving or operating machinery.

4.8 Undesirable effects

This section provides information based on all adverse reactions from clinical trials, post-marketing studies or spontaneous reports. The most frequently reported adverse reactions are injection site reactions, asthenia, nausea, and increased hepatic enzymes (ALT, AST, ALP).

The following frequency categories for adverse drug reactions (ADRs) were calculated based on the Faslodex 500 mg treatment group in pooled safety analyses of the CONFIRM (Study D6997C00002), FINDER 1 (Study D6997C00004), FINDER 2 (Study D6997C00006), and NEWEST (Study D6997C00003) studies that compared Faslodex 500 mg with Faslodex 250 mg. The frequencies in the following table were based on all reported adverse drug reactions, regardless of the investigator assessment of causality.

Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency groupings are defined according to the following convention: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$). Within each frequency grouping adverse reactions are reported in order of decreasing seriousness.

Table 1 Adverse Drug Reactions

Adverse reactions by system organ class and frequency		
Infections and infestations	Common	Urinary tract infections
Immune system disorders	Common	Hypersensitivity reactions
Metabolism and nutrition disorders	Common	Anorexia ^a
Nervous system disorders	Common	Headache
Vascular disorders	Common	Venous thromboembolism ^a , hot flushes
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting, diarrhoea
Hepatobiliary disorders	Very common	Increased hepatic enzymes (ALT, AST, ALP) ^a
	Common	Elevated bilirubin ^a
	Uncommon	Hepatic failure ^c , hepatitis ^c , elevated gamma-GT
Skin and subcutaneous tissue disorders	Common	Rash
Musculoskeletal and connective tissue disorders	Common	Back pain ^a
Reproductive system and breast disorders	Uncommon	Vaginal moniliasis, leukorrhea, vaginal haemorrhage
General disorders and administration site conditions	Very common	Asthenia ^a , injection site reactions ^b
	Uncommon	Injection site haemorrhage, injection site haematoma

^a Includes adverse drug reactions for which the exact contribution of Faslodex cannot be assessed due to the underlying disease.

^b The term injection site reactions does not include the terms injection site haemorrhage and injection site haematoma.

^c The event was not observed in major clinical studies (CONFIRM, FINDER 1, FINDER 2, NEWEST). The frequency has been calculated using the upper limit of the 95% confidence interval for the point

estimate. This is calculated as 3/563 (where 563 is the number of patients in the major clinical studies), which equates to a frequency category of 'uncommon'.

4.9 Overdose

There is no human experience of overdose. Animal studies suggest that no effects other than those related directly or indirectly to anti-estrogenic activity were evident with higher doses of fulvestrant (see section 5.3). If overdose occurs, symptomatic supportive treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Endocrine therapy, Anti-estrogens, ATC code: L02BA03

Mechanism of action and pharmacodynamic effects

Fulvestrant is a competitive estrogen receptor (ER) antagonist with an affinity comparable to estradiol. Fulvestrant blocks the trophic actions of estrogens without any partial agonist (estrogen-like) activity. The mechanism of action is associated with down-regulation of estrogen receptor protein levels. Clinical trials in postmenopausal women with primary breast cancer have shown that fulvestrant significantly down-regulates ER protein in ER positive tumours compared with placebo. There was also a significant decrease in progesterone receptor expression consistent with a lack of intrinsic estrogen agonist effects. It has also been shown that fulvestrant 500 mg downregulates ER and the proliferation marker Ki67, to a greater degree than fulvestrant 250 mg in breast tumours in postmenopausal neoadjuvant setting.

Clinical safety and efficacy in advanced breast cancer

A phase III clinical trial was completed in 736 postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. The study included 423 patients whose disease had recurred or progressed during anti-estrogen therapy (AE subgroup) and 313 patients whose disease had recurred or progressed during aromatase inhibitor therapy (AI subgroup). This trial compared the efficacy and safety of Faslodex 500 mg (n=362) with Faslodex 250 mg (n=374). Progression-free survival (PFS) was the primary endpoint; key secondary efficacy endpoints included objective response rate (ORR), clinical benefit rate (CBR) and overall survival (OS). Efficacy results for the CONFIRM study are summarized in Table 2.

Table 2 Summary of results of the primary efficacy endpoint (PFS) and key secondary efficacy endpoints in the CONFIRM study

Variable	Type of estimate; treatment comparison	Faslodex 500 mg (N=362)	Faslodex 250 mg (N=374)	Comparison between groups (Faslodex 500 mg/Faslodex 250 mg)		
				Hazard ratio	95% CI	p-value
PFS	K-M median in months; hazard ratio					
All Patients		6.5	5.5	0.80	0.68, 0.94	0.006
-AE subgroup (n=423)		8.6	5.8	0.76	0.62, 0.94	0.013
-AI subgroup (n=313) ^a		5.4	4.1	0.85	0.67, 1.08	0.195
OS^b	K-M median in months; hazard ratio					
All Patients		26.4	22.3	0.81	0.69, 0.96	0.016 ^c
-AE subgroup (n=423)		30.6	23.9	0.79	0.63, 0.99	0.038 ^c

-AI subgroup (n=313) ^a		24.1	20.8	0.86	0.67, 1.11	0.241 ^c
Variable	Type of estimate; treatment comparison	Faslodex 500 mg (N=362)	Faslodex 250 mg (N=374)	Comparison between groups (Faslodex 500 mg/Faslodex 250 mg)		
				Absolute difference in %	95% CI	
ORR ^d	% of patients with OR; absolute difference in %					
All Patients		13.8	14.6	-0.8	-5.8, 6.3	
-AE subgroup (n=296)		18.1	19.1	-1.0	-8.2, 9.3	
-AI subgroup (n=205) ^a		7.3	8.3	-1.0	-5.5, 9.8	
CBR ^e	% of patients with CB; absolute difference in %					
All Patients		45.6	39.6	6.0	-1.1, 13.3	
-AE subgroup (n=423)		52.4	45.1	7.3	-2.2, 16.6	
-AI subgroup (n=313) ^a		36.2	32.3	3.9	-6.1, 15.2	

^a Faslodex is indicated in patients whose disease had recurred or progressed on an anti-estrogen therapy.

The results in the AI subgroup are inconclusive.

^b OS is presented for the final survival analyses at 75% maturity.

^c Nominal p-value with no adjustments made for multiplicity between the initial overall survival analyses at 50% maturity and the updated survival analyses at 75% maturity.

^d ORR was assessed in patients who were evaluable for response at baseline (ie, those with measurable disease at baseline: 240 patients in the Faslodex 500 mg group and 261 patients in the Faslodex 250 mg group).

^e Patients with a best objective response of complete response, partial response or stable disease ≥ 24 weeks.

PFS:Progression-free survival; ORR:Objective response rate; OR:Objective response; CBR:Clinical benefit rate; CB:Clinical benefit; OS:Overall survival; K-M:Kaplan-Meier; CI:Confidence interval; AI:Aromatase inhibitor; AE:Anti-estrogen.

Two phase III clinical trials were completed in a total of 851 postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. 77% of the study population had estrogen receptor positive breast cancer. These trials compared the safety and efficacy of monthly administration of Faslodex 250 mg versus the daily administration of 1 mg anastrozole (aromatase inhibitor). Overall, Faslodex at the 250 mg monthly dose was at least as effective as anastrozole in terms of progression-free survival, objective response, and time to death. There were no statistically significant differences in any of these endpoints between the two treatment groups. Progression-free survival was the primary endpoint. Combined analysis of both trials showed that 83% of patients who received Faslodex progressed, compared with 85% of patients who received anastrozole. Combined analysis of both trials showed the hazard ratio of Faslodex 250 mg to anastrozole for progression-free survival was 0.95 (95% CI 0.82 to 1.10). The objective response rate for Faslodex 250 mg was 19.2% compared with 16.5% for anastrozole. The median time to death was 27.4 months for patients treated with Faslodex and 27.6 months for patients treated with anastrozole. The hazard ratio of Faslodex 250 mg to anastrozole for time to death was 1.01 (95% CI 0.86 to 1.19).

Effects on the postmenopausal endometrium

Preclinical data do not suggest a stimulatory effect of fulvestrant on the postmenopausal endometrium (see section 5.3). A 2-week study in healthy postmenopausal volunteers treated with 20 µg per day ethinylestradiol showed that pre-treatment with Faslodex 250 mg resulted in significantly reduced stimulation of the postmenopausal endometrium, compared to pre-treatment with placebo, as judged by ultrasound measurement of endometrium thickness.

Neoadjuvant treatment for up to 16 weeks in breast cancer patients treated with either Faslodex 500 mg or Faslodex 250 mg did not result in clinically significant changes in endometrial thickness, indicating a lack of agonist effect. There is no evidence of adverse endometrial effects in the breast cancer patients studied. No data are available regarding endometrial morphology.

In two short-term studies (1 and 12 weeks) in premenopausal patients with benign gynaecologic disease, no significant differences in endometrial thickness were observed by ultrasound measurement between fulvestrant and placebo groups.

Effects on bone

There are no long-term data on the effect of fulvestrant on bone. Neoadjuvant treatment for up to 16 weeks in breast cancer patients with either Faslodex 500 mg or Faslodex 250 mg did not result in clinically significant changes in serum bone-turnover markers.

Paediatric population

Faslodex is not indicated for use in children. The European Medicines Agency has waived the obligation to submit the results of studies with Faslodex in all subsets of the paediatric population in breast cancer (see section 4.2 for information on paediatric use).

An open-label phase II study investigated the safety, efficacy and pharmacokinetics of fulvestrant in 30 girls aged 1 to 8 years with Progressive Precocious Puberty associated with McCune Albright Syndrome (MAS). The paediatric patients received 4 mg/kg monthly intramuscular dose of fulvestrant. This 12-month study investigated a range of MAS endpoints and showed a reduction in the frequency of vaginal bleeding and a reduction in the rate of bone age advancement. The steady-state trough concentrations of fulvestrant in children in this study were consistent with that in adults (see section 5.2). There were no new safety concerns arising from this small study, but 5-year data are yet not available.

5.2 Pharmacokinetic properties

Absorption

After administration of Faslodex long-acting intramuscular injection, fulvestrant is slowly absorbed and maximum plasma concentrations (C_{max}) are reached after about 5 days. Administration of Faslodex 500 mg regimen achieves exposure levels at, or close to, steady state within the first month of dosing (mean [CV]: AUC 475 [33.4%] ng.days/ml, C_{max} 25.1 [35.1%] ng/ml, C_{min} 16.3 [25.9%] ng/ml, respectively). At steady state, fulvestrant plasma concentrations are maintained within a relatively narrow range with up to an approximately 3-fold difference between maximum and trough concentrations. After intramuscular administration, the exposure is approximately dose-proportional in the dose range 50 to 500 mg.

Distribution

Fulvestrant is subject to extensive and rapid distribution. The large apparent volume of distribution at steady state (V_{dss}) of approximately 3 to 5 l/kg suggests that distribution is largely extravascular. Fulvestrant is highly (99%) bound to plasma proteins. Very low density lipoprotein (VLDL), low density lipoprotein (LDL), and high density lipoprotein (HDL) fractions are the major binding components. No interaction studies were conducted on competitive protein binding. The role of sex hormone-binding globulin (SHBG) has not been determined.

Biotransformation

The metabolism of fulvestrant has not been fully evaluated, but involves combinations of a number of possible biotransformation pathways analogous to those of endogenous steroids. Identified metabolites (includes 17-ketone, sulphone, 3-sulphate, 3- and 17-glucuronide metabolites) are either less active or exhibit similar activity to fulvestrant in anti-estrogen models. Studies using human liver preparations and recombinant human enzymes indicate that CYP3A4 is the only P450 isoenzyme involved in the oxidation of fulvestrant; however, non-P450 routes appear to be more predominant *in vivo*. *In vitro* data suggest that fulvestrant does not inhibit CYP450 isoenzymes.

Elimination

Fulvestrant is eliminated mainly in metabolised form. The major route of excretion is via the faeces, with less than 1% being excreted in the urine. Fulvestrant has a high clearance, 11 ± 1.7 ml/min/kg, suggesting a high hepatic extraction ratio. The terminal half-life ($t_{1/2}$) after intramuscular administration is governed by the absorption rate and was estimated to be 50 days.

Special populations

In a population pharmacokinetic analysis of data from phase III studies, no difference in fulvestrant's pharmacokinetic profile was detected with regard to age (range 33 to 89 years), weight (40-127 kg) or race.

Renal impairment

Mild to moderate impairment of renal function did not influence the pharmacokinetics of fulvestrant to any clinically relevant extent.

Hepatic impairment

The pharmacokinetics of fulvestrant has been evaluated in a single-dose clinical trial conducted in subjects with mild to moderate hepatic impairment (Child-Pugh class A and B). A high dose of a shorter duration intramuscular injection formulation was used. There was up to about 2.5-fold increase in AUC in subjects with hepatic impairment compared to healthy subjects. In patients administered Faslodex, an increase in exposure of this magnitude is expected to be well tolerated. Subjects with severe hepatic impairment (Child-Pugh class C) were not evaluated.

Paediatric population

The pharmacokinetics of fulvestrant has been evaluated in a clinical trial conducted in 30 girls with Progressive Precocious Puberty associated with McCune Albright Syndrome (see section 5.1). The paediatric patients were aged 1 to 8 years and received 4 mg/kg monthly intramuscular dose of fulvestrant. The geometric mean (standard deviation) steady state trough concentration ($C_{min,ss}$) and AUC_{ss} was 4.2 (0.9) ng/mL and 3680 (1020) ng*hr/mL, respectively. Although the data collected were limited, the steady-state trough concentrations of fulvestrant in children appear to be consistent with those in adults.

5.3 Preclinical safety data

The acute toxicity of fulvestrant is low.

Faslodex and other formulations of fulvestrant were well tolerated in animal species used in multiple dose studies. Local reactions, including myositis and granulomata at the injection site were attributed to the vehicle but the severity of myositis in rabbits increased with fulvestrant, compared to the saline control. In toxicity studies with multiple intramuscular doses of fulvestrant in rats and dogs, the anti-estrogenic activity of fulvestrant was responsible for most of the effects seen, particularly in the female reproductive system, but also in other organs sensitive to hormones in both sexes. Arteritis involving a range of different tissues was seen in some dogs after chronic (12 months) dosing.

In dog studies following oral and intravenous administration, effects on the cardiovascular system (slight elevations of the S-T segment of the ECG [oral], and sinus arrest in one dog [intravenous]) were seen. These occurred at exposure levels higher than in patients ($C_{max} > 15$ times) and are likely to be of limited significance for human safety at the clinical dose.

Fulvestrant showed no genotoxic potential.

Fulvestrant showed effects upon reproduction and embryo/foetal development consistent with its anti-estrogenic activity, at doses similar to the clinical dose. In rats, a reversible reduction in female fertility and embryonic survival, dystocia and an increased incidence of foetal abnormalities including tarsal flexure were observed. Rabbits given fulvestrant failed to maintain pregnancy. Increases in

placental weight and post-implantation loss of foetuses were seen. There was an increased incidence of foetal variations in rabbits (backwards displacement of the pelvic girdle and 27 pre-sacral vertebrae).

A two-year oncogenicity study in rats (intramuscular administration of Faslodex) showed increased incidence of ovarian benign granulosa cell tumours in female rats at the high dose, 10 mg/rat/15 days and an increased incidence of testicular Leydig cell tumours in males. In a two-year mouse oncogenicity study (daily oral administration) there was an increased incidence of ovarian sex cord stromal tumours (both benign and malignant) at doses of 150 and 500 mg/kg/day. At the no-effect level for these findings, systemic exposure levels (AUC) were, in rats, approximately 1.5-fold the expected human exposure levels in females and 0.8-fold in males, and in mice, approximately 0.8-fold the expected human exposure levels in both males and females. Induction of such tumours is consistent with pharmacology-related endocrine feedback alterations in gonadotropin levels caused by anti-estrogens in cycling animals. Therefore these findings are not considered to be relevant to the use of fulvestrant in postmenopausal women with advanced breast cancer.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol (96 per cent)
Benzyl alcohol
Benzyl benzoate
Castor oil

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store and transport in a refrigerator (2°C - 8°C).

Temperature excursions outside 2°C - 8°C should be limited. This includes avoiding storage at temperatures exceeding 30°C, and not exceeding a 28 day period where the average storage temperature for the product is below 25°C (but above 2°C - 8°C). After temperature excursions, the product should be returned immediately to the recommended storage conditions (store and transport in a refrigerator 2°C - 8°C). Temperature excursions have a cumulative effect on the product quality and the 28 day time period must not be exceeded over the duration of the 4-year shelf life of Faslodex (see section 6.3). Exposure to temperatures below 2°C will not damage the product providing it is not stored below - 20°C.

Store the pre-filled syringe in the original package in order to protect from light.

6.5 Nature and contents of container

BD SafetyGlide is a trademark of Becton Dickinson and Company and is CE-marked: CE 0050.

The pre-filled syringe presentation consists of:

One clear type 1 glass pre-filled syringe with polystyrene plunger rod, fitted with a tamper-evident closure, containing 5 ml Faslodex solution for injection.

A safety needle (BD SafetyGlide™) for connection to the barrel is also provided.

Or

Two clear type 1 glass pre-filled syringes with polystyrene plunger rod, fitted with a tamper-evident closure, each containing 5 ml Faslodex solution for injection. Safety needles (BD SafetyGlide™) for connection to each barrel are also provided.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

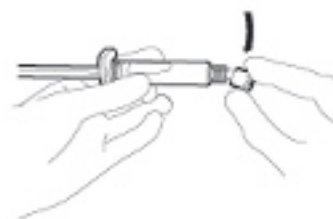
Instructions for administration

Warning - Do not autoclave safety needle (BD SafetyGlide Shielding Hypodermic Needle) before use. Hands must remain behind the needle at all times during use and disposal.

For each of the two syringes:

- Remove glass syringe barrel from tray and check that it is not damaged.
- Break the seal of the white plastic cover on the syringe Luer connector Luer-Lok to remove the cover with the attached rubber tip cap (see Figure 1).

Figure 1



- Peel open the safety needle (BD SafetyGlide) outer packaging. Attach the safety needle to the Luer-Lok (see Figure 2).
- Twist until firmly seated.
- Twist to lock the needle to the Luer connector.
- Pull shield straight off needle to avoid damaging needle point.
- Transport filled syringe to point of administration.
- Remove needle sheath.
- Parenteral solutions must be inspected visually for particulate matter and discolouration prior to administration.
- Expel excess gas from the syringe.

Figure 2



- Administer intramuscularly slowly (1-2 minutes/injection) into the buttock. For user convenience, the needle bevel- up position is oriented to the lever arm (see Figure 3).

Figure 3



- After injection, immediately apply a single-finger stroke to the activation assisted lever arm to activate the shielding mechanism (see Figure 4).
NOTE: Activate away from self and others. Listen for click and visually confirm needle tip is fully covered.

Figure 4



Disposal

Pre-filled syringes are for single use **only**.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited
Alderley Park
Macclesfield
Cheshire
SK10 4TG
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/269/001

EU/1/03/269/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 March 2004

Date of latest renewal: 10 March 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

AstraZeneca UK Limited
Silk Road Business Park,
Macclesfield, SK10 2NA
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP .

An updated RMP shall be submitted annually until renewal.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Faslodex 250 mg solution for injection.
fulvestrant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled syringe contains 250 mg fulvestrant in 5 ml solution

3. LIST OF EXCIPIENTS

Ethanol (96 per cent), benzyl alcohol, benzyl benzoate and castor oil. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a pre-filled syringe.

1 pre-filled syringe (5 ml)
1 safety needle
2 pre-filled syringes (5 ml each)
2 safety needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use.
For single use only.
For full instructions on the administration of Faslodex and the use of the safety needle see enclosed, Instructions for administration.
Two syringes must be administered to receive the 500 mg recommended monthly dose.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport in a refrigerator.

Store the pre-filled syringe in the original package in order to protect from light. See package leaflet for information on temperature excursions.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited
Alderley Park
Macclesfield
Cheshire
SK10 4TG
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/269/001

EU/1/03/269/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

Faslodex 250 mg solution for injection
fulvestrant
IM use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

5 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Faslodex 250 mg solution for injection

Fulvestrant

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Faslodex is and what it is used for
2. What you need to know before you use Faslodex
3. How to use Faslodex
4. Possible side effects
5. How to store Faslodex
6. Contents of the pack and other information

1. What Faslodex is and what it is used for

Faslodex contains the active substance fulvestrant, which belongs to the group of estrogen blockers. Estrogens, a type of female sex hormones, can in some cases be involved in the growth of breast cancer.

Faslodex is used to treat advanced or metastatic breast cancer in postmenopausal women.

2. What you need to know before you use Faslodex

Do not use Faslodex

- if you are allergic to fulvestrant or to any of the other ingredients of this medicine (listed in section 6 'What Faslodex contains')
- if you are pregnant or breast-feeding
- if you have severe liver problems

Warnings and precautions

Tell your doctor if any of these apply to you:

- kidney or liver problems
- low numbers of platelets (which help blood clotting) or bleeding disorders
- previous problems with blood clots
- osteoporosis (loss of bone density)
- Alcoholism

Children and adolescents

Faslodex is not indicated in children and adolescents under 18 years.

Other medicines and Faslodex

Please tell your doctor, nurse or pharmacist if you are taking or have recently taken any other medicines.

In particular, you should tell your doctor if you are using anticoagulants (medicines to prevent blood clots).

Pregnancy and breast-feeding

You must not use Faslodex if you are pregnant. If you can become pregnant, you should use effective contraception while being treated with Faslodex.

You must not breast-feed while on treatment with Faslodex.

Driving and using machines

Faslodex is not expected to affect your ability to drive or use machines. However, if you feel tired after treatment do not drive or use machines.

Faslodex contains 10% w/v ethanol (alcohol), i.e. up to 1000 mg per dose, equivalent to 20 ml beer or 8 ml wine per dose.

Harmful for those suffering from alcoholism.

To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.

3. How to use Faslodex

The recommended dose is 500 mg fulvestrant (two 250 mg/5 ml injections) given once a month with an additional 500 mg dose given 2 weeks after the initial dose.

Your doctor or nurse will give you Faslodex as a slow intramuscular injection, one into each of your buttocks.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

You may need immediate medical treatment if you experience any of the following side effects:

- Allergic (hypersensitivity) reactions, including swelling of the face, lips, tongue and/or throat
- Thromboembolism (increased risk of blood clots)*
- Inflammation of the liver (hepatitis)
- Liver failure

Tell your doctor, pharmacist, or nurse if you notice any of the following side effects:

Very common side effects (may affect more than 1 in 10 people)

- Injection site reactions, such as pain and/or inflammation
- Abnormal levels of liver enzymes (in blood tests)*
- Nausea (feeling sick)
- Weakness, tiredness*

All other side effects:

Common side effects (may affect up to 1 in 10 people)

- Headache
- Hot flushes
- Vomiting, diarrhoea, or loss of appetite*
- Rash

- Urinary tract infections
- Back pain*
- Increase of bilirubin (bile pigment produced by the liver)
- Thromboembolism (increased risk of blood clots)*
- Allergic (hypersensitivity) reactions, including swelling of the face, lips, tongue and/or throat

Uncommon side effects (may affect up to 1 in 100 people)

- Vaginal bleeding, thick, whitish discharge and candidiasis (infection)
- Bruising and bleeding at the site of injection
- Increase of gamma-GT, a liver enzyme seen in a blood test
- Inflammation of the liver (hepatitis)
- Liver failure

* Includes side effects for which the exact role of Faslodex cannot be assessed due to the underlying disease.

If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Faslodex

Store and transport in a refrigerator (2°C - 8°C).

Temperature excursions outside 2°C - 8°C should be limited. This includes avoiding storage at temperatures exceeding 30°C, and not exceeding a 28 day period where the average storage temperature for the product is below 25°C (but above 2°C - 8°C). After temperature excursions, the product should be returned immediately to the recommended storage conditions (store and transport in a refrigerator 2°C - 8°C). Temperature excursions have a cumulative effect on the product quality and the 28 day time period must not be exceeded over the duration of the 4-year shelf life of Faslodex . Exposure to temperatures below 2°C will not damage the product providing it is not stored below – 20°C.

Keep the pre-filled syringe in the original package, in order to protect from light.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton or syringe labels after the abbreviation EXP. The expiry date refers to the last day of that month.

Your health care professional will be responsible for the correct storage, use and disposal of Faslodex.

6. Contents of the pack and other information

What Faslodex contains

- The active substance is fulvestrant. Each pre-filled syringe (5 ml) contains 250 mg fulvestrant.
- The other ingredients (excipients) are ethanol (96 per cent), benzyl alcohol, benzyl benzoate and castor oil.

What Faslodex looks like and contents of the pack

Faslodex is a clear, colourless to yellow, viscous solution in a pre-filled syringe fitted with a tamper-evident closure, containing 5 ml solution for injection. Two syringes must be administered to receive the 500 mg recommended monthly dose.

Faslodex has 2 pack presentations, either a pack containing 1 glass pre-filled syringe or a pack containing 2 glass pre-filled syringes. Safety needles (BD SafetyGlide™) for connection to each barrel are also provided.

Not all pack sizes may be marketed.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Faslodex 500 mg (2 x 250 mg/5 ml solution for injection) should be administered using two pre-filled syringes, see section 3.

BD SafetyGlide is a trademark of Becton Dickinson and Company and is CE-marked: CE 0050.

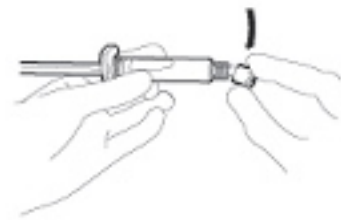
Instructions for administration

Warning - Do not autoclave safety needle (BD SafetyGlide™ Shielding Hypodermic Needle) before use. Hands must remain behind the needle at all times during use and disposal.

For each of the two syringes:

- Remove glass syringe barrel from tray and check that it is not damaged.
- Break the seal of the white plastic cover on the syringe Luer connector Luer-Lok to remove the cover with the attached rubber tip cap (see Figure 1).

Figure 1



- Peel open the safety needle (BD SafetyGlide) outer packaging. Attach the safety needle to the Luer-Lok (see Figure 2).
- Twist until firmly seated.
- Twist to lock the needle to the Luer connector.
- Pull shield straight off needle to avoid damaging needle point.
- Transport filled syringe to point of administration.
- Remove needle sheath.
- Parenteral solutions must be inspected visually for particulate matter and discolouration prior to administration.
- Expel excess gas from the syringe.

Figure 2



- Administer intramuscularly slowly (1-2 minutes/injection) into the buttock. For user convenience, the needle bevel- up position is oriented to the lever arm (see Figure 3).

Figure 3



- After injection, immediately apply a single-finger stroke to the activation assisted lever arm to activate the shielding mechanism (see Figure 4).
NOTE: Activate away from self and others. Listen for click and visually confirm needle tip is fully covered.

Figure 4



Disposal

Pre-filled syringes are for single use **only**.

Any unused product or waste material should be disposed of in accordance with local requirements.